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(54) Title: A DENDRITIC MACROMOLECULE AND A PROCESS THEREOF

(57) Abstract: The present invention is in relation to a dendritic molecule having symmetrically sited branches having four or more generations of dendrimers wherein the branch points are tertiary amines linked together with oxygen atom of ether and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker. In addition the invention also provides a process to prepare such dendritic macromolecules.

A DENDRITIC MACROMOLECULE AND A PROCESS THEREOF.

FIELD OF INVENTION

The present invention is in relation to dendritic macromolecules. More particularly, the present invention is in relation to establishing constitutionally new dendritic macromolecules, presenting many surface functional groups, each functional group presenting a unique reactivity pattern. These new dendritic macromolecules are capable of acting as base platforms for further modifications, aided by, for example, surface functional groups or the defined inner cavities present within these dendritic macromolecules.

BACKGROUND AND PRIOR ART OF THE INVENTION

Dendritic macromolecules represent a new type of polymeric architecture, which has become popular in a variety of studies, including application level, in the last two decades. The branches-upon-branches is an unique architectural feature of these macromolecules and they enjoy being the most monodispersed of all synthetic macromolecules.

The systematic studies of the dendritic macromoleules may be traced back first to the series of the so-called poly (amido amine) or Starburst dendrimers, pioneered by Tomalia and co-workers, Polym. J. (Tokyo), 117 (1985), U.S.Pat. No.4,507,466; U.S.Pat. No.4,558,320 and U.S.Pat. No. 4,737,550. These dendrimers possess primarily an amide as the linkage unit and a tertiary amine as the branch point. Another popular dendritic macromolecular series is the poly (propylene imine) dendrimers, advanced by Meijer and de Brabander-van den Berg, Angew. Chem. Int. Ed. Engl. 1308 (1993), WO

93/14147, U.S. Pat. No. 5,698,662. In this poly(propylene imine) dendrimer series, there is no heteroatom or linker functionalities between the branch points, that are constituted by tertiary amines. The branch points are separated typically by alkylene units. Other popular dendrimers studied extensively, are by Fréchet and co-workers, J. Am. Chem. Soc. 7638 (1990); Majoral and co-workers, Science, 1981 (1997) and Fréchet and co-workers U.S. Pat. No. 5,041,516. Low molecular weight poly (propyl ether imine) dendritic molecules with ether linkages and imine branch points wherein the molecular weight is less than 3600 g/mol, with ester units at the surfaces has been described in, Rama Krishna and Jayaraman, J. Org. Chem. 2003, 9694. Although four and higher generation dendrimers were highly desired as the same has more versatility than an third and lower generation dendrimers, it was found that fourth and higher generation dendrimers could not be constructed by the protocol that yielded dendrimers up to three generations.

Each dendrimer is characterized by its unique constitution and thus attendant physico-chemical and biological properties differ significantly. Although there exists a number of dendrimers, the ones that have been utilized in a wide range of studies remain limited. The poly(amido amine) and poly(propylene imine) dendrimers are the most studied dendritic macromolecules, in general. Due to the physico-chemical properties that reside with the molecular constitution of the dendrimers, identification of new monomers and synthesis of new dendrimers are important target areas in the branch of polymer/macromolecular science and technology. It is also necessary to achieve higher and higher generational dendrimers as each such higher generation dendrimer improves the scope of application of such dendrimers. A large number of technologically important utilities such as those in power, energy, healthcare, medical, engineering,

consumer goods, environmental, electronics and optoelectronics are expected to benefit by the unique architectural characteristics of the dendritic macromolecules.

OBJECTS OF THE PRESENT INVENTION

The principal object of the present invention is in relation to preparation of dendritic macromolecules with four or more generations; the said dendrimers being with ether linkages and tertiary amine branch points.

SUMMARY OF INVETNION

Accordingly, the present invention provides a dendritic macromolecule having symmetrically sited branches, wherein the branch points are tertiary amines, the branches linked together through linkers comprising oxygen atom corresponding to an ether, and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker; and a process for preparing a dendritic macromolecule of four generations or more comprises steps of: reacting the alcohol units of the lower dendritic molecule to react with molar equivalents of α,β-unsaturated nitrile, in the presence of an alkali, to install nitrile groups at the surfaces of the dendritic macromolecule; converting the nitrile groups at the surfaces of the dendritic macromolecule to the corresponding amines, mediated by supported metal catalysts and hydrogen gas; subjecting the resulting amine functional groups to react with α,β-unsaturated esters; converting the ester units present at the surfaces of the dendritic macromolecule to the corresponding alcohol units, mediated by metal hydride reagents; to prepare a higher generation dendritic molecule wherein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is in relation to a dendritic macromolecule having symmetrically sited branches, wherein the branch points are tertiary amines, the branches linked together through linkers comprising oxygen atom corresponding to an ether, and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker.

In another embodiment of the present invention, wherein the number of symmetrically sited branches, are ranging from 3 to 8 and the number of peripheral groups ranging from 16 to 512.

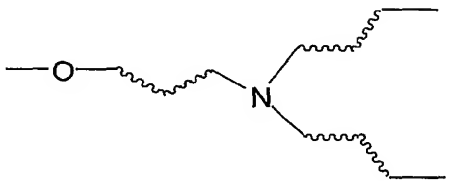
In yet another embodiment of the present invention, wherein the substituents on the linkers are selected from a group comprising an alkyl, branched alkyl and aryl group.

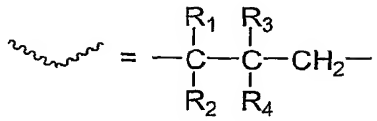
In still another embodiment of the present invention, wherein the alkyl, branched alkyl and aryl substituents in the linear three methylene linker are present on two adjacent methylene groups and the third unsubstituted methylene group is present on left to the heteroatoms.

In still another embodiment of the present invention, wherein the functional group present at the periphery of the dendritic macromolecule is selected from a group comprising alcohol, amine, ester, nitrile and carboxylic acid or a combination thereof.

In still another embodiment of the present invention, wherein said molecule is useful in the delivery of drug molecules, fragrant molecules, antibodies, antigens, nucleotides, nucleosides, peptides, proteins and as lubricants in automotive oils.

In still another embodiment of the present invention, wherein repeating unit of the dendritic macromolecule is:



where 

R_1, R_2, R_3, R_4 = H, alkyl, aryl

The present invention is in relation to a process for preparing a dendritic macromolecule comprises steps of,

i. reacting the alcohol units of the lower dendritic molecule to react with molar equivalents of α,β-unsaturated nitrile, in the presence of an alkali, to install nitrile groups at the surfaces of the dendritic macromolecule;

ii. converting nitrile groups at the surfaces of the dendritic macromolecule to the corresponding amines, mediated by supported metal catalysts and hydrogen gas;

iii. subjecting the resulting amine functional groups to react with α,β-unsaturated esters.

iv. converting ester units present at the surfaces of the dendritic macromolecule to the corresponding alcohol units, mediated by metal hydride reagents; to prepare a higher generation dendritic molecule; wherein construction of fourth and higher generation dendrimer is enabled by one or more of additional inventive process steps. In one embodiment of the present invention, the lower dendritic molecule is one generation lower than the target dendritic molecule.

In another embodiment of the present invention, the molar equivalents of α,β-unsaturated nitrile is 4-50 molar equivalent per unit of the hydroxyl group present in the dendritic molecule.

In yet another embodiment of this invention, the excess of α,β-unsaturated nitrile is added in instalments are an interval. In a preferred embodiment, the addition is made in three instalments, one at the beginning, second at an interval of 8 hours from first addition and third at 15 hours after second addition.

In still another embodiment of the present invention, the alkali used is 40% aqueous solution of sodium hydroxide;

In still another embodiment of the present invention, wherein the catalyst is selected from a group of metal supported catalysts such as Raney alloys; preferably Raney Cobalt.

In still another embodiment of the present invention, the concentration of nitrile ranges between 0.01 mM and 4.0 mM.

In still another embodiment of the present invention, the metal hydride reagent is selected from a range of metal hydride reagents preferably lithium aluminum hydride.

In still another embodiment of the present invention, by-products 2-cyano ethanol and bis-nitrile are removed from reaction mixture by a combination of liquid:liquid extraction and distillation before the higher generation dendrimer is subjected to further addition of next generation.

In still another embodiment of the present invention the four and higher generation dendrimers are applied in the delivery of drug molecules, fragrant molecules,

antibodies, antigens, nucleotides, nucleosides, peptides, proteins and as lubricant in automotive oils.

The innovation deals with the preparation of dendritic macromolecules wherein the characteristics of the general framework / scheme / sequence of steps of process of production of the preparation comprises (i) reaction of an α,β-unsaturated nitrile with a compound presenting a number of hydroxyl groups at the surfaces, in the presence of an alkali; (ii) reduction of the compound resulting from step (i) to a compound containing several symmetrically substituted amine functional groups, by supported metal catalysts; (iii) reacting the compound resulting from step (ii) with an α,β-unsaturated ester, leading to the formation of several symmetrically substituted ester functional groups at the surfaces; (iv) subjecting the compound resulting from step (iii) to a reduction reaction with a metal hydride based reagent, so as to form a product with several symmetrically substituted hydroxyl group containing dendritic macromolecule. The number of the hydroxyl group present in the dendritic macromolecule, after the above four steps, is to a maximum of twice that number present in the compound used in step (i).

This invention describes dendritic macromolecules with a well-defined chemical constitution. The chemical constitution comprises a linkage group and a branching group. The presence of both the linkage group and the branching group are required simultaneously in the chemical constitution of the dendritic macromolecules of this invention. An α,β-unsaturated ester and a nitrile act as the monomers. These two types of monomers are taken through covalent bond formation and subsequent functional group conversions. While the covalent bond formations create the unique linkage and the branching groups, the functional group conversion generates a different

functional group capable of undergoing the covalent bond formation, leading to the formation of the linkage and branching groups. The functional group conversions and the covalent bond formations are conducted alternatively to prepare the dendritic macromolecules of the present invention.

Every symmetrically sited branching group is considered to constitute a generation. Thus the branching group nearest to the central atom or unit or the core of the dendritic structure is treated as the first generation. The next symmetrically placed branching groups are treated to complete the second generation dendritic structure. The progressive next symmetrically placed branching groups are treated to complete the third generation dendritic structure and so on. With the branching group multiplicity of 2 and the central atom or unit or core of the dendritic macromolecule multiplicity of 2, the maximum number of surface groups possible in each generation is twice the number that is present in the corresponding immediate lower generation dendritic structure. Thus, the first generation dendritic structure with 2 symmetrically placed branching groups can have at the maximum 4 surface functionalities or units; the second generation dendritic structure with 4 symmetrically placed branching groups can have at the maximum 8 surface functionalities or units; the third generation dendritic structure with 8 symmetrically placed branching groups can have at the maximum 16 surface functionalities or units; the fourth generation dendritic structure with 16 symmetrically placed branching groups can have at the maximum 32 surface functionalities or units; the fifth generation dendritic structure with 32 symmetrically placed branching groups can have at the maximum 64 surface functionalities or units; the sixth generation dendritic structure with 64 symmetrically placed branching groups can have at the maximum 128 surface functionalities or units; the seventh generation dendritic structure with 128 symmetrically placed branching groups can have at the

maximum 256 surface functionalities or units and the eighth generation dendritic structure with 256 symmetrically placed branching groups can have at the maximum 512 surface functionalities or units.

The functionalities, that undergo covalent bond formation upon reaction with nitriles and esters in the present invention, are primarily alcohols and amines. These functional groups are generated in prior reactions through the type chemical reactions called functional group conversions.

The low molecular weight dendritic scaffolds disclosed by Rama Krishna & Jayaraman (2003) are incorporated as a reference, in the present invention. Repetitive and consecutive reactions, corresponding to the conversion of (i) esters to alcohols; (ii) alcohols to ethers, possessing pendant nitriles; (iii) nitriles to primary amines and (iv) primary amines to tertiary amines, possessing pendant esters, constitute to be the integral steps involved in the construction of the dendritic macromolecules of Rama Krishna & Jayaraman (2003) which were reported to have been constructed up to three generations by convergent as well as divergent construction strategy. However, further to third generation construction by the protocol given by Rama Krishna & Jayaraman (2003), although four generation dendrimer or higher generation dendrimer was highly desired as the same has more versatility than an third generation dendrimer, it was found that fourth generation dendrimer or higher could not be constructed by straightforward application of the protocol that yielded up to three generations. Further work was undertaken to establish fourth generation and higher generation dendrimers. In addition to the invention of a series of new dendritic macromolecules, invention relating to the improvements of the protocol adopted in Rama Krishan & Jayaraman (2003) were also achieved. A substantial part of the accomplishments are published in

the publication "Synthesis of large generation poly(ether imine) (PETIM) dendrimers", Jayamurugan, G,; Jayaraman, N. *Tetrahedron* 2006,*62*, 9582-9588 (publication date August 17, 2006) and also forms subject matter of this patent application.

Since dendrimers with generations higher than three were highly desired on account of their higher efficiency for the intended applications, work was undertaken to establish dendrimers higher than three generations and, in the process, find out what improvements are needed in the protocol adopted by Rama Krishna & Jayaraman (2003) so that fourth and higher generations can be constructed. This invention also covers the improvements made in the protocol to enable construction of four generations and higher dendrimers, at least up to 8th generation where the branch points are tertiary amines, the branches are linked together through linkers comprising oxygen atom corresponding to an ether, and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker. This invention also covers dendrimers where the branch points are tertiary amines, the branches are linked together through linkers comprising oxygen atom corresponding to an ether, and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker, and having four to eight generations, including eighth generation. This invention also covers dendrimers where the branch points are tertiary amines, the branches are linked together through linkers comprising oxygen atom corresponding to an ether, and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker, and having more than eight generations that can be constructed using the process of this invention.

This invention also includes an embodiment wherein a dendrimer having branch points as tertiary amines, the branches being linked together through linkers comprising oxygen atom corresponding to an ether, and the heteroatoms being separated by a substituted or non-substituted linear three methylene linker have, on their surface, one or more of a functional group selected from an alcohol, amine, nitrile, ester or carboxyl functional group in a pure single type functional group or as a mixture of combinations.

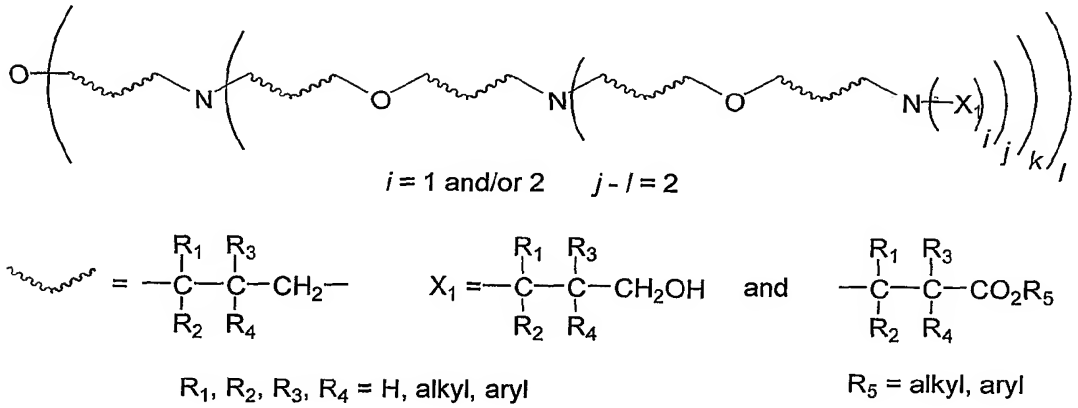
The repetitive and consecutive reactions of the present invention are performed by (i) α,β-unsaturated ester and nitrile as monomers and (ii) supported metal catalysts and metal hydrides as the reagents.

Examples of α,β-unsaturated esters are linear and branched alkyl esters and aryl esters, the most preferred among them is tert-butyl acrylate. Example of α,β-unsaturated nitriles are a series of alkyl and aryl substituted acrylonitriles, the most preferred among them is unsubstituted acrylonitrile.

Embodiments of this invention comprising the products as well as process steps of this invention are as follows:

In the first embodiment of the invention, the low molecular weight dendritic scaffolds of molecular weight less than 3600 g mol^{-1}, with ester units present at the surfaces, as described in Rama Krishna and Jayaraman (2003) are used as the initiator to construct the dendritic macromolecules. The number of ester units at the peripheries varies between 4 and 16, depending on the chosen low molecular weight dendritic scaffold. Accordingly, the molecular weights of the dendritic scaffolds are in the range of 600-3600 g mol^{-1}. The functional group conversion, namely, a reduction, provides alcohol functionalities at the peripheries, the number of such groups vary between 4 and 16.

Formula 1 describes the structure of the dendritic macromolecule of this embodiment 1 as:



Formula 1

According to the formula 1, the product of the third generation dendritic structure contains *x* number of alcohol units and 16-*x* number of ester units present at the surfaces of the dendritic macromolecules. More preferably, the product in formula 1 contains 16 alcohol units. When this generation is targeted for the synthesis of next higher generation through subsequent steps, the presence of 16 alcohol units in this generation is essential. In addition to the example given above, the larger generation dendritic macromolecules of this invention contain hydroxyl units in the progression (i) *x* number of alcohol units in the fourth generation dendritic structure and 32-*x* number of ester units, with more preferable *x* being 32; (ii) *x* number of alcohol units in the fifth generation dendritic structure and 64-*x* number of ester units, with more preferable *x* being 64; (iii) *x* number of alcohol units in the sixth generation dendritic structure and 128-*x* number of ester units, with more preferable *x* being 128; (iv) *x* number of alcohol units in the seventh generation dendritic structure and 256-*x* number of ester units, with more preferable *x* being 256; (v) *x* number of alcohol units in the eighth generation

dendritic structure and 512-x number of ester units, with more preferable x being 512. In general when each of the generation is targeted for the synthesis of the next higher generation through subsequent steps, then the presence of the maximum number of alcohol units is essential in that generation.

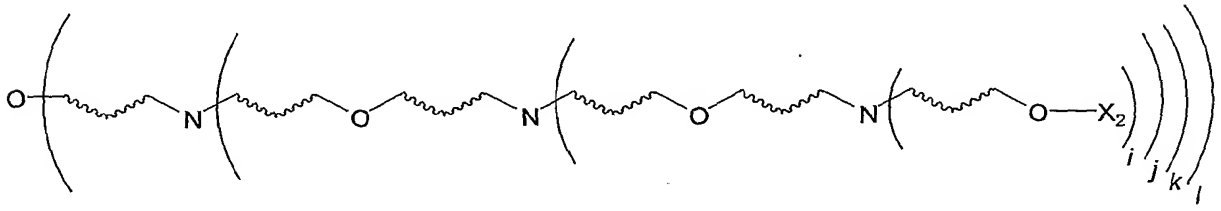
The reduction reaction was achieved with total conversion from ester to alcohol when 1.3 molar equivalents of a metal hydride per unit of ester was used by Rama Krishna & Jayaraman (2003). However, the same conversion of surface ester groups to surface alcohol groups achieved under same conditions was only partial and not total and such a dendrimer was not fit for addition of fourth generation. To ensure that reduction of functional groups at the periphery to alcohol is total, it was found that addition of at least 2 molar equivalents of metal hydride were added per unit of ester.

The reduction of esters to alcohols is performed in a solvent and in the presence of a metal hydride. Suitable metal hydrides are lithium aluminium hydride, alkyl derivatives of lithium aluminium hydride, combination of lithium borohydride and $AlCl_3$. The preferable metal hydride among these is lithium aluminium hydride. The solvents for the reduction are THF (tetrahydrofuran), diethyl ether, dioxane, toluene and hexanes. The most preferable solvent is THF. The molar ratio of metal hydride generally is 0.5 to 4 per one ester unit, the preferable molar ratio of the metal hydride is 2 per unit of ester to ensure complete conversion.

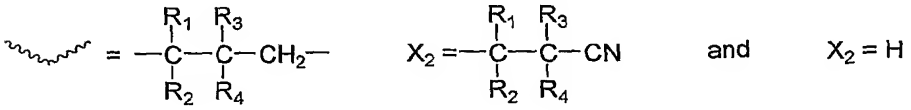
After the conversion of the surface ester functionalities to alcohol functionalities, in the protocol of Rama Krishna & Jayaraman (2003), the reaction mixture containing the product could be straight away subjected to further step of reiterative reaction. For the objective of constructing fourth generation, however, the same protocol failed to work. Further reiterative reaction worked for adding fourth or higher generation only after

isolation of the pure product from the reaction mixture. This isolation may be done by various methods. In this invention, the said isolation was achieved by differential solubility. When lithium aluminium hydride is used as the reducing agent, the byproducts LiOH and $Al(OH)_3$, arising after the work-up of the reaction, are removed by: (i) washing the crude product with water; (ii) filtration; (iii) removal of water under reduced pressure; (iv) washing the product with MeOH; (v) filtration; (vi) removal of MeOH under reduced pressure and (vii) extraction of the product with $CHCl_3$ and removal of the solvents under reduced pressure. If required, the above process is repeated to eliminate any inorganic byproducts that may still remain.

The dendritic macromolecules fully carrying alcohol functionalities at the surfaces are proceeded further to generate larger dendritic structure, through reaction of the alcohol functionalities with α, β-unsaturated nitriles. This reaction provides saturated β-cyano ethyl ethers, wherein the alcohol units are converted to β-cyano ethyl ethers. Formula 2 provides an example of the second embodiment of the invention, as follows:



i = 1 and/or 2 *j* - *l* = 2



R_1, R_2, R_3, R_4 = H, alkyl, aryl **Formula 2**

According to the formula 2, the product contains x number of nitrile units and 16-x number of alcohol units present at the surfaces of the dendritic macromolecules. More preferably, the product in formula 2 contains 16 nitrile units. When this generation is targeted for the synthesis of next higher generation through subsequent steps, the presence of 16 nitrile units in this generation is essential. In addition to the example given above, the larger generation dendritic macromolecules of this invention contain nitrile units in the progression (i) x number of nitrile units in the fourth generation dendritic structure and 32-x number of alcohol units, with more preferable x being 32; (ii) x number of nitrile units in the fifth generation dendritic structure and 64-x number of alcohol units, with more preferable x being 64; (iii) x number of nitrile units in the sixth generation dendritic structure and 128-x number of alcohol units, with more preferable x being 128; (iv) x number of nitrile units in the seventh generation dendritic structure and 256-x number of alcohol units, with more preferable x being 256; (v) x number of nitrile units in the eighth generation dendritic structure and 512-x number of alcohol units, with more preferable x being 512.

In general when each of the generation is targeted for the synthesis of the next higher generation through subsequent steps, then the presence of the maximum number of nitrile units is essential in that generation.

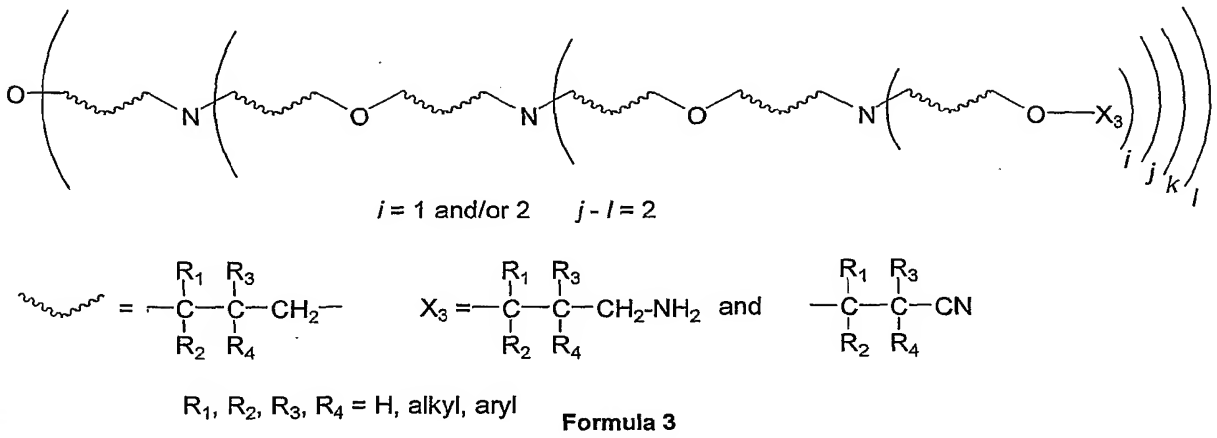
The reaction of the conversion of the alcohol functionalities to the nitrile functionalities requires the presence of an alkali and a solvent. The alkalis that can be used include NaOH, KOH, $Ca(OH)_2$ and $Mg(OH)_2$. The most preferred among these alkalis is an aqueous solution of NaOH.

Up to third generation, conversion of alcohol surface functionalities to the nitrile functionalities achieved was total and easily achieved when 1.25 molar equivalents of nitrile were used, added in one single lot and reaction time was 6 hours. This molar equivalent was, however, not sufficient for ensuring total conversion for fourth and higher generations. The need to add more equivalents of acrylonitrile could perhaps be because the higher generations encounter a progressively increasing steric hindrance at the reactive sites present in the peripheries and more equivalents of the reagents help to drive the reaction to completion. It was seen that in order to ensure total conversion of alcohol to nitriles in fourth generation and above, at least 4 molar equivalents or more of the nitrile were required per unit of the hydroxyl group; and that too not in one single lot but in divided lots added at an interval. Thus, one lot is added in the initial stage, one more after several hours, one more lot after several hours. The reaction time was several hours, or a couple of days for the fourth or higher generations.

It was also found out that for the reaction to proceed further for addition of fourth generation and higher generations, it was necessary that the by-products, bis(cyanoethyl ether) and 2-cyano ethanol were removed by liquid-liquid extraction by hexane and methanol-water mixture, and further by column chromatography. In absence of this step too, the separation of the higher generation dendrimer from the by-product was not possible.

In the subsequent preparations, the nitrile functionalities present at the surfaces of dendrimers are proceeded through a functional group conversion, by which the nitrile functionalities are converted to primary amine functionalities through a reduction using supported metal catalysts, such as Raney alloys, the more preferable among the Raney alloys being Raney cobalt.

Formula 3 provides an example of the third embodiment of the present invention, as follows:



Formula 3

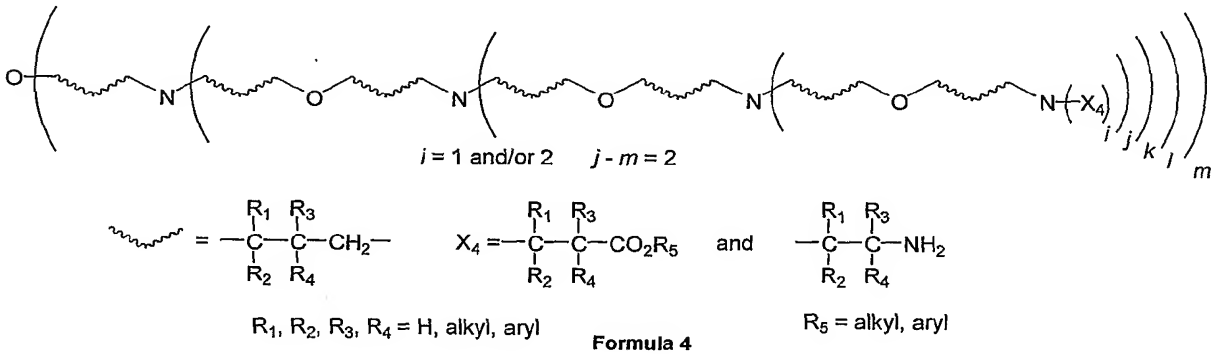
Upto third generation, the reduction of nitrile functionalities to primary amine was fully achievable by using a concentration of above 6 mM of nitrile compound in water. These conditions did not work for construction of fourth generation and above and for that purpose.- The reduction reaction of the higher generations is found to require much lower concentrations than the reduction of lower generations. The higher concentration of the solution for the higher generation do not lead to a clean reaction, thereby preventing the progress of the synthesis. The concentration of the nitrile compound in water that worked for fourth and higher generation dendrimer synthesis is between 0.01-4.0 mM, more preferably between 0.1-0.4 mM and the weight ratio of the nitrile compound to the supported metal catalyst is generally 1:15 and, most preferably in the range of 1:3 to 1:7. The substantially nitrile functionalized dendritic macromolecules are subjected to reduction, using supported metal catalysts, such as Raney alloys, the more preferable among the Raney alloys being Raney cobalt. The reduction requires

positive pressure of hydrogen gas, maintained at a higher pressure. The reaction is conducted in water, an alcohol such as MeOH may be added if required.

The hydrogen gas pressure is generally in the range of 20-70 atm, more preferably between 40-50 atm. The reaction temperature is generally maintained between 60-85 °C, more preferably at ~ 70 °C. After the reaction, the supported metal catalyst can be removed by filtration. Alternatively, a magnetic pellet picker can be used to remove the catalyst.

According to the formula 3, the product contains *x* number of amine units and 16-*x* number of nitrile units present at the surfaces of the dendritic macromolecules. More preferably, the product in formula 3 contains 16 amine units. When this generation is targeted for the synthesis of next higher generation through subsequent steps, the presence of 16 amine units in this generation is essential. In addition to the example given above, the larger generation dendritic macromolecules of this invention contain amine units in the progression (i) *x* number of amine units in the fourth generation dendritic structure and 32-*x* number of nitrile units, with more preferable *x* being 32; (ii) *x* number of amine units in the fifth generation dendritic structure and 64-*x* number of nitrile units, with more preferable *x* being 64; (iii) *x* number of amine units in the sixth generation dendritic structure and 128-*x* number of nitrile units, with more preferable *x* being 128; (iv) *x* number of amine units in the seventh generation dendritic structure and 256-*x* number of nitrile units, with more preferable *x* being 256; (v) *x* number of amine units in the eighth generation dendritic structure and 512-*x* number of nitrile units, with more preferable *x* being 512. In general when each of the generation is targeted for the synthesis of the next higher generation through subsequent steps, then the presence of the maximum number of amine units is essential in that generation.

In the fourth embodiment of the invention, the amine functionalities present in the surface of the dendritic macromolecules are subjected through a chemical reaction with an α,β-unsaturated ester, leading to the formation of ester functionalities at the surfaces. The number of ester functionalities thus formed will be up to twice the number of amine functionalities present in the starting material of this reaction. Formula 4 provides an example of this embodiment of invention, as follows:



Formula 4

It is preferable that all the amine functionalities on the surface are converted to ester functionalities, at least when a fifth generation is desired to be added to this fourth generation denrimer. However, if addition of fifth generation is not the objective, it is conceivable that, as a matter of preference or otherwise, on account of incomplete reactions, both the functionalities i.e. primary amine and ester shall be present on the surface in varying proportions.

According to the formula 4, the product contains *x* number of ester units and 32-*x* number of amine units present at the surfaces of the dendritic macromolecules. More preferably, the product in formula 4 contains 32 ester units. When this generation is targeted for the synthesis of next higher generation through subsequent steps, the

presence of 32 ester units in this generation is essential. In addition to the example given above, the larger generation dendritic macromolecules of this invention contain ester units in the progression (i) *x* number of ester units in the fourth generation dendritic structure and 32-*x* number of amine units, with more preferable *x* being 32; (ii) *x* number of ester units in the fifth generation dendritic structure and 64-*x* number of amine units, with more preferable *x* being 64; (iii) *x* number of ester units in the sixth generation dendritic structure and 128-*x* number of amine units, with more preferable *x* being 128; (iv) *x* number of ester units in the seventh generation dendritic structure and 256-*x* number of amine units, with more preferable *x* being 256; (v) *x* number of ester units in the eighth generation dendritic structure and 512-*x* number of amine units, with more preferable *x* being 512.

In general when each of the generation is targeted for the synthesis of the next higher generation through subsequent steps, then the presence of the maximum number of ester units is essential in that generation.

The products formed in each step in the last cycle of iterative reactions can be stopped to provide the dendritic macromolecules with defined functionality at the surfaces.

The amine resulting from the above step is taken through reaction with an α,β-unsaturated esters, the most preferable ester being tert-butyl acrylate. Alcoholic solvents can be used generally to conduct the reaction of amine functionalized dendrimers, the most preferable solvent is MeOH. Addition of 3.33 molar equivalents of t-butyl acrylate per unit of amine worked very well upto construction of three generations. However, for fourth generation construction, this molar ratio led to less t-butyl ester substituted dendritic product and formation of polymer-like polar impurity leading to formation of less t-substituted ester substituted product which can not be

considered further for higher generation dendrimer. The ratio of tert-butyl acrylate to each amine functionalities present at the surfaces of the dendritic macromolecule required for satisfactory conversion is in excess of 3.33:1 up to to 200:1. Most preferable ratio is in the range of 5-60 molar equivalent of tert-butyl acrylate per one unit of amine present at the surfaces.

At the end of the reaction, the excess tert-butyl acrylate can be recovered by distillation. Column chromatography, using neutral alumina matrix, of the crude product is carried out usually to obtain the pure ester functionalized dendritic macromolecules.

The embodiments 1-4 described above are necessary to complete the constitution of the dendritic macromolecules of the present invention. Thus, each cycle involves a set of four distinct reactions to complete the cycle. Thus, initiating from a low molecular weight dendritic molecule with 16 ester functionalities at the surfaces requires full five cycles to reach a dendritic macromolecule presented with 512 ester functionalities at the surfaces, wherein complete reactivities of the functional groups occurred at the surfaces of the dendritic macromolecule.

The dendritic macromolecules of this invention can be used in many applications. Various applications, in such areas as, medical, healthcare, environmental, catalysis, engineering, electronics and opto-electronics are targeted for promotion of better performances, characteristics and efficiencies through the dendrimer technology.

The important molecular feature available for the dendritic macromolecules is the presence of large of number of dense peripheral functional groups. This large number of peripheral functional groups provides the opportunity for attaching, for example, drug molecules, fragrant molecules, antibodies, antigens, nucleotides, nucleosides, peptides, proteins and carbohydrate ligands *etc.* Also, the low viscosity of the dendritic

macromolecules, in comparison to random polymers of the similar molecular weights, may find applications in the area of, for example, lubricants in automotive oils.

Another important physical attribute of these new class of dendrimers is that their radius is considerably larger than dendrimers of the type as described in U.S.Pat. No.4,507,466; U.S.Pat. No.4,558,320 and U.S.Pat. No. 4,737,550, relating to the poly(amido amine) series of dendrimers and WO 93/14147, U.S. Pat. No. 5,698,662, relating to the poly(propylene imine) series of dendrimers. The radius of a particular generation of the dendrimers of the present invention would relate to next higher generation of, for example, the poly(amido amine) dendrimers. This important physical attribute of the dendrimers of the present invention originates from the larger linkers lengths, connecting the branch functionalities. The utility of the larger radius of the dendrimers, with attendant lesser molecular weights, can be envisaged in applications such as drug delivery. The dendritic base platforms with larger sizes and lesser molecular weights will have beneficial effects upon conjugation with drugs. The larger through-bond distances between the branch functionalities of the present invention also allow them to be more flexible and less rigid. The presence of ether and amine functionalities of the dendrimers of this invention makes them analogous to the functionalities present individually in polymers such as poly(ethylene glycol) and poly(ethylene imine). The lower toxicity profile of these types of functionalities make the molecules derived from thereof to be invoked in applications, such as, drug delivery vehicles, drug formulations, skin care formulations, gene delivery vehicles, vehicles for conjugation with pharmacologically important nucleosides, nucleotides, peptides, proteins, carbohydrates and other synthetic agents. The series of the dendrimers have defined internal voids and cavities that can encapsulate small molecules, relevant in, for example, enhancing the bioavailability of a drug, or a drug encapsulation or a toxic

chemical encapsulation or a biocide encapsulation *etc.* Thus, from the point of view of various applications, lower generation dendrimers of the present invention can be utilized in place of higher generation dendrimers of the type as described in above disclosures, in order, for example, to avoid toxicity towards biological objects.

The technology of the instant Application is further elaborated with the help of following examples. However, the examples should not be construed to limit the scope of the invention.

Throughout this specification, unless the context does not permit that meaning, mention of a singular, with or without the phrase "one or more of" shall include pleural also of the same or any of functional equivalent of the same, any homologue or analogue of the same and also includes mention of any one of a homologue or an analogue them or more of them separately or in a combination. Thus, mention of "alkyl" includes mention of any one or more than one amongst methyl, ethyl, propyl and the like either separately or in a combination; mention of "frangrance" includes any one or more of a fragrant molecule either separately or in combination. Conversely, unless context does not permit, use of a plural also includes mention of a singular or any one of a homologue or analogue or equivalent of the same. Thus mention of "functional groups" includes use of only one functional group also or any functional group capable of discharging equivalent function if the illustrated functional group is replaced by a functional group which is not specifically illustrated in the specification. Further, description of the embodiments, examples, compositions described in this specification are for the illustrative purpose only and are not to be construed to limit the scope of subject matter that is inherent in the claims and any variations that are obvious to a person skilled in the art and any possible equivalent and capable of meeting the claimed

invention and not expressly mentioned in this specification are also construed to be included within the scope of claims.

Example : 1

A mixture of the 16-alcohol functionalized dendritic macromolecule (5.0 g) and of aq 40 % NaOH (0.4 mL) was added with acrylonitrile (2.15 mL), at 0 °C and stirred at room temperature for 15 h. Additional amount of acrylonitrile (2.15 mL) was added portion wise, and this additional amount was added again after 8 h of stirring and the reaction was monitored (TLC alumina matrix; eluant: 6 % MeOH/ $CHCl_3$, R_f of the required 16-nitrile functionalized dendritic macromolecule: 0.45). The solution was filtered through celite using chloroform, and washed with water and the solvents evaporated under reduced pressure. The crude reaction mixture was dissolved in aqueous MeOH, subjected to liquid-liquid extraction with hexane to remove ~70 % of bis(2-cyano ethyl ether). Finally, the reaction mixture was subjected to column chromatography (neutral alumina, 100-300 mesh size), afforded the 16-nitrile functionalized dendritic macromolecule, as a colorless gummy liquid. Yield: 6.33 g.

Example : 2

In a 2 L hydrogenation reactor vessel, a mixture of sixteen nitrile-functionalized dendritic macromolecule (1.5 g) in distilled water (1.2 L) and Raney Co (Aldrich Inc. USA) (4.0 g) was hydrogenated in the presence of hydrogen gas (46 atm.). The temperature was maintained in the range of 70-75 °C. After 3.5 h, the reaction mixture was cooled and the spent Raney cobalt was recovered using a magnetic pellet picker. Methanol was added to wash the compound from catalyst and to remove the catalyst from pellet picker, flushed with water and the water layer was concentrated at 55 °C under reduced pressure. For easy removal of water, azeotrope mixture was formed by

adding dioxane solvent and evaporated quickly. To the resulting reaction mixture methanol was added and filtered. The filtrate was concentrated and dried to afford the corresponding 16 amine-functionalized dendritic macromolecule. Yield: 1.53 g.

Example : 3

A solution of 16 amine terminated dendritic macromolecule (1.53 g) in methanol (50 mL) and tert-butyl acrylate (filtered through pad of alumina prior to the addition) (10 mL) was stirred vigorously for 72 h. The reaction was monitored (TLC alumina matrix, eluant: 3 % MeOH/ $CHCl_3$, R_f of the 32 ester functionalized dendritic macromolecule: 0.52). Excess *tert*-butyl acrylate and methanol were removed under reduced pressure after completion of the reaction. Addition of petroleum ether helped to precipitate the polar impurity and it was separated by filtration through filter paper. Subsequent evaporation of the solvent afforded the 32 ester terminated dendritic macromolecule. Further purification was performed by column chromatography (neutral alumina; eluant: $CHCl_3$: MeOH), to afford the 32 ester functionalized dendritic macromolecule. Yield: 3.15 g.

Example : 4

A solution of 32-ester functionalized dendrimer (4.0 g) in THF (150 mL) was added dropwise to a suspension of $LiAlH_4$ (1.34 g) in THF (50 mL), over a period of 15 min at 0 °C and the stirring was continued for 4 h at room temperature. After completion of the reaction, the mixture was cooled to 0 °C, quenched with ice, diluted with water, passed through celite, and the filtrate concentrated under reduced pressure. The crude reaction mixture was added with MeOH, filtered, and the filtrate concentrated. The resulting reaction mixture was extracted $CHCl_3$. Removal of the solvents afforded the 32-alcohol functionalized dendritic macromolecule. Yield: 2.76 g.

Example : 5

A mixture of the 32-alcohol functionalized dendritic macromolecule (5.0 g) and of aq 40 % NaOH (0.4 mL) was added with acrylonitrile (2.02 mL), at 0 °C and stirred at room temperature for 15 h. Additional amount of acrylonitrile (2.02 mL) was added portion wise, and this additional amount was added again after 8 h of stirring and the reaction was monitored (TLC alumina matrix; eluant: 6 % MeOH/ $CHCl_3$, R_f of the required 32-nitrile functionalized dendritic macromolecule: 0.6). The solution was filtered through celite using chloroform, and washed with water and the solvents evaporated under reduced pressure. The crude reaction mixture was dissolved in aqueous MeOH-H_2O (~ 70:30), subjected to liquid-liquid extraction with hexane to remove ~70 % of bis(2-cyano ethyl ether). Finally, the reaction mixture was subjected to column chromatography (neutral alumina, 100-300 mesh size), to afford the 32-nitrile functionalized dendritic macromolecule, as a colorless gummy liquid. Yield: 5.23 g.

Example : 6

In a 2 L hydrogenation reactor vessel, a mixture of 32 nitrile-functionalized dendritic macromolecule (1.0 g) in distilled water (1.2 L) and Raney Co (Aldrich Inc. USA) (5.0 g) was hydrogenated in the presence of hydrogen gas (46 atm.). The temperature was maintained in the range of 70-75 °C. After 3.5 h, the reaction mixture was cooled and the spent Raney cobalt was recovered using a magnetic pellet picker. Methanol was added to wash the compound from catalyst and to remove the catalyst from pellet picker, flushed with water and the water layer was concentrated at 55 °C under reduced pressure. For easy removal of water, azeotrope mixture was formed by adding dioxane solvent and evaporated quickly. To the resulting reaction mixture methanol was added

and filtered. The filtrate was concentrated and dried to afford the corresponding 32 amine-functionalized dendritic macromolecule. Yield: 1.01 g.

Example : 7

A solution of 32 amine terminated dendritic macromolecule (1.01 g) in methanol (50 mL) and tert-butyl acrylate (filtered through pad of alumina prior to the addition) (10 mL) was stirred vigorously for 72 h. The reaction was monitored (TLC alumina matrix, eluant: 3 % MeOH/ $CHCl_3$, R_f of the 64 ester functionalized dendritic macromolecule: 0.66). Excess *tert*-butyl acrylate and methanol were removed under reduced pressure after completion of the reaction. Addition of petroleum ether helped to precipitate the polar impurity and it was separated by filtration through filter paper. Subsequent evaporation of the solvent afforded the 64 ester terminated dendritic macromolecule. Further purification was performed by column chromatography (neutral alumina; eluant: $CHCl_3$: MeOH), to afford the 64 ester functionalized dendritic macromolecule. Yield: 1.70 g.

Example 8: Synthesis of 32-salicylate ester functionalized dendritic macromolecule:

To a mixture of methyl salicylate (1.90 g, 12.5 mmol) and $NaHCO_3$ (1.2 g) in 1,2-dimethoxy ethane (40 mL), a solution of 32-chloride functionalized dendritic macromolecule (1.50 g, 0.26 mmol) in 1,2-dimethoxy ethane (30 mL) was added at 0 °C, stirred at room temperature for 12 h. The reaction mixture was filtered, the filtrate evaporated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (50 mL), washed with water, dried and evaporated to afford 32-salicylate ester functionalized dendritic macromolecule. Yield: 2.65 g.

CLAIMS

1. A dendritic macromolecule, wherein the branch points are tertiary amines, the branches linked together through linkers comprising oxygen atom of an ether, and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker, wherein the said dendritic macromolecule has four or more generations.

2. A dendritic macromolecule of claim 1, where the number of functional groups at the surface being equal to 16 to at least $n = (4X\ 2^y)$, where "n" is number of functional groups at surface of a dendrimer generation, "X" is symbol for multiplication and "y" is number of functional groups at surface of the immediate previous generation the functional groups on the surface being uniformly of one of alcohol, nitrile, primary amine, ester, carboxyl or a mixture of any two or more; accordingly a number of functional groups at the surface being at least equal to 16 for third generation, 32 for fourth generation, 64 for fifth generation, 128 for sixth generation, 256 for seventh generation, 512 for eighth generation and the like.

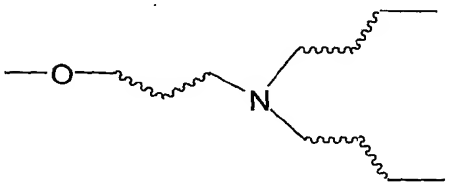
3. The dendritic macromolecule as claimed in claim 1, wherein the number of symmetrically sited branches, are ranging from 3 to 8 and the number of peripheral groups ranging from 16 to at least 512.

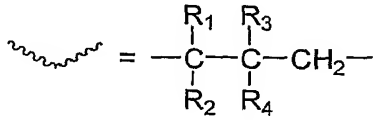
4. The dendritic macromolecule as claimed in claim 1, wherein the substituents on the three methylene linkers are selected from a group comprising an alkyl, branched alkyl and aryl group.

5. The dendritic macromolecule as claimed in claim 1, wherein the alkyl, branched alkyl and aryl substituents in the linear three methylene linker are present on

two adjacent methylene groups and the third unsubstituted methylene group is present on left to the heteroatoms.

6. The dendritic macromolecule as claimed in claim 1, wherein repeating unit of the dendritic macromolecule is:



where 

R_1, R_2, R_3, R_4 = H, alkyl, aryl

7. A process for preparing a dendritic macromolecule having substantially symmetrically sited branches, wherein the branch points are tertiary amines, the branches linked together through linkers comprising oxygen atom of an ether, and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker, wherein the said dendritic macromolecule had four or more generations of dendrons, comprising reiterative steps of:

a. reacting the alcohol units of the lower dendritic molecule to react with molar equivalents of α,β-unsaturated nitrile, in the presence of an alkali, to install nitrile groups at the surfaces of the dendritic macromolecule, wherein (i) at least about 4 molar equivalents or more of nitrile units were required per unit of the hydroxyl group, (ii) the reagent containing nitrile was added in more than one lots at time intervals, (iii) the reaction was carried out for more than six hours, (iv) the product having nitrile groups on surface was isolated from the by-products and then subjected to next step of reaction;

b. converting nitrile groups at the surfaces of the dendritic macromolecule to the corresponding amines, mediated by supported metal catalysts and hydrogen gas; wherein (i) the concentration of the nitrile compound in water is between 0.01-4.0 mM, more preferably between 0.1-0.4 mM and (ii) the weight ratio of the nitrile compound to the supported metal catalyst is generally 1:15 and, most preferably in the range of 1:3 to 1:7

c. subjecting the resulting amine functional groups to react with α,β-unsaturated esters; wherein the ratio of ester units to each unit of amine functionalities present at the surfaces of the dendritic macromolecule required for satisfactory conversion is in excess of 3.33:1 up to 200:1, most preferable ratio is in the range of 5-60 molar equivalent of tert-butyl acrylate per one unit of amine present at the surfaces, and

d. converting ester units present at the surfaces of the dendritic macromolecule to the corresponding alcohol units, mediated by metal hydride reagents; to prepare a higher generation dendritic molecule, wherein the molar ratio of metal hydride generally is 0.5 to 4 per one ester unit, the preferable molar ratio of the metal hydride is 2 per unit of ester and the product is isolated from reaction mixture for subjecting the same to next cycle of reiterative reactions.

8. A process of claim 8 wherein:

a. the said alkali used is 40% aqueous solution of sodium hydroxide, the said by-product in step a. of claim 8 is a bis-nitrile, the said by-product is isolated by a combination of liquid-liquid extraction and column chromatography;

b. the said the supported metal catalyst is selected from a group of metal supported catalysts such as Raney alloys; preferably Raney Cobalt;

c. the said metal hydride reagent is selected from a range of metal hydride reagents preferably lithium aluminum hydride.

9. The process as claimed in claim 8, wherein the lower dendritic molecule is one generation lower than the target dendritic molecule.

10. A composition of matter containing dendritic macromolecule of claim 1 as an ingredient and one or more of an other active ingredients.

11. A composition of claim 12 wherein the said other ingredient is one or more of a fragrance, drug, antibodies, antigens, nucleotide, nucleoside, carbohydrate, peptide, protein, biocide, lubricant and the like.

12. A dendritic molecule, a process of its preparation, and compositions containing the dendritic molecules substantially as herein described with reference to foregoing examples and drawings.

AMENDED CLAIMS
received by the International Bureau on 16 October 2008 (16.10.08); claims 1-12 replaced by amended claims 1-13

1. A dendritic macromolecule, wherein the branch points are tertiary amines, the branches linked together through linkers comprising oxygen atom of an ether, and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker, wherein the said dendritic macromolecule has four or more generations.

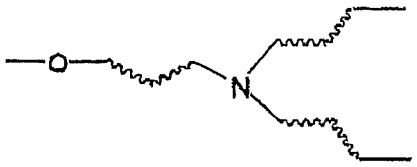
2. A dendritic macromolecule of claim 1, where the number of functional groups at the surface being equal to 16 to at least $n = (4X\ 2^{y})$, where "n" is number of functional groups at surface of a dendrimer generation, "X" is symbol for multiplication and "y" is the generation number of the immediate previous generation. The functional groups on the surface being uniformly of one of alcohol, nitrile, primary amine, ester, carboxyl or a mixture of any two or more; accordingly a number of functional groups at the surface being at least equal to 16 for third generation, 32 for fourth generation, 64 for fifth generation, 128 for sixth generation, 256 for seventh generation, 512 for eighth generation and the like.

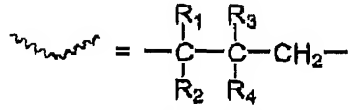
3. The dendritic macromolecule as claimed in claim 1, wherein the number of symmetrically sited branches, are ranging from 3 to 8 and the number of peripheral groups ranging from 16 to at least 512.

4. The dendritic macromolecule as claimed in claim 1, wherein the substituents on the three methylene linkers are selected from a group comprising an alkyl, branched alkyl and aryl group.

5. The dendritic macromolecule as claimed in claim 1, wherein the alkyl, branched alkyl and aryl substituents in the linear three methylene linker are present on two adjacent methylene groups and the third unsubstituted methylene group is present on left to the heteroatoms.

6. The dendritic macromolecule as claimed in claim 1, wherein repeating unit of the dendritic macromolecule is:



where 

R_1, R_2, R_3, R_4 = H, alkyl, aryl

7. A process for preparing a dendritic macromolecule having substantially symmetrically sited branches, wherein the branch points are tertiary amines, the branches linked together through linkers comprising oxygen atom of an ether, and the heteroatoms are separated by a substituted or non-substituted linear three methylene linker, wherein the said dendritic macromolecule had four or more generations of dendrons, comprising reiterative steps of:

a. reacting the alcohol units of isolated pure lower dendritic molecule to react with molar equivalents of α,β-unsaturated nitrile, in the presence of an alkali, to install nitrile groups at the surfaces of the dendritic macromolecule, wherein (i) at least about 4 molar equivalents or more of nitrile units were required per unit of the hydroxyl group, (ii) the reagent containing nitrile was added in more than one lots at time intervals, (iii) the reaction was carried out for more than six hours, (iv) the product having nitrile groups on surface was isolated from the by-products in pure form and then subjected to next step of reaction;

b. converting nitrile groups at the surfaces of the dendritic macromolecule to the corresponding amines, mediated by supported metal catalysts and hydrogen gas; wherein (i) the concentration of the nitrile compound in water is between 0.01-4.0 mM, more preferably between 0.1-0.4 mM and (ii) the weight ratio of the nitrile compound to the supported metal catalyst is generally 1:15 and, most preferably in the range of 1:3 to 1:7, (iii)

heated for at least around 3.5 hour, and (iv) the product of the reaction was isolated in pure form and then subjecting to next reiterative reaction;

c. subjecting the resulting amine functional groups to react with α,β-unsaturated esters; wherein the ratio of ester units to each unit of amine functionalities present at the surfaces of the dendritic macromolecule required for satisfactory conversion is in excess of 3.33:1 up to 200:1, most preferable ratio is in the range of 5-60 molar equivalent of tert-butyl acrylate per one unit of amine present at the surfaces, the product of the reaction was isolated in pure form and then subjecting to next reiterative reaction, and

d. converting ester units present at the surfaces of the dendritic macromolecule to the corresponding alcohol units, mediated by metal hydride reagents; to prepare a higher generation dendritic molecule, wherein the molar ratio of metal hydride generally is 0.5 to 4 per one ester unit, the preferable molar ratio of the metal hydride is 2 per unit of ester , methanol is added to wash the compound from catalyst and to remove the catalyst from pellet picker, flushed with water, dioxane added to the water layer and azeotrop of water removed by concentrating at 55 °C under reduced pressure, adding methanol to the resulting reaction mixture followed by filtration and the product is isolated from reaction mixture in pure form for subjecting the same to next cycle of reiterative reactions.

8. A process of claim 7 wherein:

a. the said alkali used is 40% aqueous solution of sodium hydroxide, the said by-product in step a. of claim 7 is a bis-nitrile, the said by-product is isolated by a combination of liquid-liquid extraction and column chromatography;

b. the said the supported metal catalyst is selected from a group of metal supported catalysts such as Raney alloys; preferably Raney Cobalt;

c. the said metal hydride reagent is selected from a range of metal hydride reagents preferably lithium aluminum hydride.

9. The process of claim 7 wherein isolation and purification of the end product of every reiterative reaction may be done on the basis of differential solubility, wherein the byproducts arising after the work-up of the reaction, are removed by: (i) washing the crude product with water; (ii) filtration; (iii) removal of water under reduced pressure; (iv) washing the product with MeOH; (v) filtration; (vi) removal of MeOH under reduced pressure and (vii) extraction of the product with $CHCl_3$ and removal of the solvents under reduced pressure, and (viii) repeating the reaction to eliminate any inorganic byproducts, if required.

10. The process as claimed in claim 7, wherein the lower dendritic molecule is one generation lower than the target dendritic molecule.

11. A composition of matter containing dendritic macromolecule of claim 1 as an ingredient and one or more of an other active ingredients.

12. A composition of claim 11 wherein the said other ingredient is one or more of a fragrance, drug, antibodies, antigens, nucleotide, nucleoside, carbohydrate, peptide, protein, biocide, lubricant and the like.

13. A dendritic molecule, a process of its preparation, and compositions containing the dendritic molecules substantially as herein described with reference to foregoing examples and drawings.

STATEMENT UNDER ARTICLE 19 (1)

The applicant humbly presents his informal response to the reasoned statement given under title **Re Item Box no. V** in the Written Opinion of the Honorable ISR Authority.

The applicant agrees with the acknowledgement by the Hon. ISR Authority that Claims nos. 4 and 5 have novelty, Inventive step and industrial applicability.

However, without agreeing with opinion of the Hon. ISR Authority on other claims, amendments have been made with a purpose to restore accuracy or to make the meaning of the claims more clear.

"As filed" claim no. 2, has been amended to delete the phrase "number of functional groups at surface" and replace it with "the generation number" This is correction of an obvious error because a person skilled in the art of dendrimer will realize that one would get astronomical number of functional groups on the surface, which are erroneous. It is this meaning of "y" that is consistent with the later part of this claim that specifically describes the number of surface functionalities for some generations viz " ---------- accordingly a number of functional groups at the surface being at least equal to 16 for third generation, 32 for fourth generation, 64 for fifth generation, 128 for sixth generation, 256 for seventh generation, 512 for eighth generation and the like."

Further the "as filed" claim nos. 7, and 8, have been amended and a new claim is inserted and numbered as claim no. 9.

As filed claim no. 7 has been amended to insert more details that existed in the description already, to make the claims more explicit and clear. No new matter is added.

"As filed" clam no. 8 is amended to replace number "8" mentioned in the claim in preamble as well as in subclaim (a) with the number "7", which is correction of an editing error and no new matter is introduced because it is clear that "as filed" claim no. 8 can not depend on claim no. 8.

A new claim no. 9 has been inserted that is based on the matter contained already in the specification and no new matter is added.

As filed claim no. 9, now renumbered as claim no. 10, has been amended to replace the claim number "8" with "7". This is also an editing error and no introduction to new matter because plain reading of as filed " claims 7 and 8 will reveal that the "as filed" claim no.9 is dependent on claim no. 7, where the antacedant to the phrase "lower dendritic molecule" is located and not on claim no. 8.

"As filed" Claim no. 10 has been renumbered as claim no. 11.

"As filed" claim no. 11 has been amended to replace the number "12" in the preamble with number "11", which has been necessitated due to insertion of a new claim at number 9 and renumbering of "as filed" claim nos. 11 and 12 to revised claim nos. 12 and 13. .

"As filed" claim no. 12 has been renumbered to revised claim no. 13.

There may be a need to amend description in view the amendments in the claims done in the context of response to the ISR under Article 19.

PCT/IN2007/000344

Box No. VIII (v) DECLARATION: NON-PREJUDICIAL DISCLOSURES OR EXCEPTIONS TO LACK OF NOVELTY

The declaration must conform to the standardized wording provided for in Section 215; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (v). If this Box is not used, this sheet should not be included in the request.

Declaration as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4.17(v) and 51*bis*.1(a)(v)):

in relation to this International Application No. PCT/IN2007/...../CHE

INDIAN INSTITUTE OF SCIENCE declares that the subject matter claimed in this International Application was disclosed as follows :

(i) publication
(ii) date of disclosure August 17, 2006.
(iii) title of disclosure "Synthesis of large generation poly(propyl ether imine) (PETIM) dendrimers"
(iv) place of disclosure available online at www.sciencedirect.com.
(v) this declaration is made for the purpose of all designation.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (v)".

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2007/000344

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C08G 73/02 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPIDS, JAPIO, CAPLUS: & keywords: dendrit, hyperbranch, amine, etherimine, nitrile, & similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JAYAMURUGAN, G. et al. Synthesis of large generation poly(propyl ether imine) (PETIM) dendrimers. Tetrahedron. 2006, vol 62, pages 9582-9588 See the whole document	1-3, 6-12
X	KRISHNA, T. et al. Synthesis of Poly(propyl ether imine) Dendrimers and Evaluation of Their Cytotoxic Properties. J. Org. Chem. 2003, vol 68, pages 9694-9704 See the whole document	1-3, 6-12
X	KRISHNA, T. et al. Synthesis and biological evaluation of 3-amino-propan-1-ol based poly(ether imine) dendrimers. Tetrahedron. 2005, vol 61, pages 4281-4288 See the whole document	1-3, 6-12

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
07 December 2007

Date of mailing of the international search report 11 DEC 2007

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2007/000344

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2002/020469 A1 (POHANG IRON & STEEL CO LTD et al) 14 March 2002 See the whole document	
A	US 2006/0165601 A1 (JOSEPHK et al) 27 July 2006 See the whole document	
A	WO 2007/006700 A1 (JANSSEN PHARMACEUTICA NV) 18 January 2007 See the whole document	
A	US 5698662 A (STOELWINDER et al) 16 December 1997 See the whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN2007/000344

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	0220469	EP	1317422	KR	2002001932	US	2003199577
US	2006165601	JP	2006188683				
WO	2007006700						
US	5698662	AU	33691/93	AU	73914/94	BE	1007260
		BG	98106	BR	9303946	BR	9407013
		CA	2105967	CA	2166720	CN	1129455
		CZ	9301884	CZ	9600038	EP	0575596
		EP	0707611	EP	0741756	FI	933984
		FI	960080	HU	66443	HU	72476
		NL	9200043	NO	960006	NZ	246697
		NZ	269602	PL	312435	SK	1696
		SK	97893	US	5530092	US	5610268
		WO	9314147	WO	9502008	WO	9520619

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX